Sex-specific Epidemiology of Heart Failure Risk and Mortality in Europe: Results from the BiomarCaRE Consortium

Brief Title: Sex differences in heart failure

Christina Magnussen, MD; Teemu J. Niiranen, MD, PhD; Francisco M. Ojeda, PhD; Francesco Gianfagna, MD, PhD; Stefan Blankenberg, MD; Erkki Vartiainen, MD, PhD; Susana Sans, MD, PhD; Gerard Pasterkamp, MD, PhD; Maria Hughes, PhD; Simona Costanzo, PhD; Maria Benedetta Donati, MD, PhD; Pekka Jousilahti, MD, PhD; Allan Linneberg, MD, PhD; Tarja Palosaari, MSc; Giovanni de Gaetano, MD, PhD; Martin Bobak, MD, MSc, PhD; Hester M den Ruijter, PhD; Torben Jørgensen, MD, PhD; Stefan Söderberg, MD, PhD; Kari Kuulasmaa, PhD; Tanja Zeller, PhD; Licia Iacoviello, MD, PhD; Veikko Salomaa, MD, PhD; Renate B. Schnabel, MD, MSc on behalf of the BiomarCaRE Consortium

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Department of General and Interventional Cardiology, University Heart Center Hamburg, Germany (C.M., F.M.O., S.B., T.Z., R.B.S.); DZHK (German Center for Cardiovascular Research), partner site Hamburg/Kiel/Luebeck, Germany (C.M., S.B., T.Z., R.B.S.); Division of Medicine, Turku University Hospital and University of Turku, Finland *(T.J.N.); Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy (F.G., S.C., M.B.D., G.d.G., L.I.); EPIMED Research Center, Department of Medicine and Surgery, University of Insubria, Varese, Italy (F.G., L.I.); National Institute for Health and Welfare, Helsinki, Finland (T.J.N., E.V., P.J., T.P., K.K., V.S.); Catalan Department of Health, Barcelona, Spain (S. Sans); Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, Netherlands (G.P.); Center of Excellence for Public Health, Institute of Clinical Sciences, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland (M.H.); Center for Clinical research and Prevention, Frederiksbergs, Denmark (A.L.); Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark (A.L.); Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (A.L., T.J.); Department of Epidemiology and Public Health, University College London, UK (M.B.); Laboratory of Experimental Cardiology, University Medical Center Utrecht, Netherlands (H.M.d.R.); Research Center for Prevention and*

Health, Glostrup University Hospital, Denmark (T.J.); Faculty of Medicine, Aalborg University, Denmark (T.J.); Department of Public Health and Clinical Medicine, and Heart Centre, Umeå University, Sweden (S. Söderberg)

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Address for correspondence:
Renate B. Schnabel
University Heart Center Hamburg-Eppendorf
Martinistrasse 52, 20246 Hamburg
Email: r.schnabel@uke.de
Fax: +49 40 7410 53622
Phone: +49 15222816064

ABSTRACT

Objectives: Differences between sexes in HF risk and mortality are investigated.

Background: Sex differences in heart failure (HF) epidemiology are insufficiently understood.

Methods: In 78657 individuals (median age 49.5 years, age range 24.1 to 98.7 years, 51.7% women) from community-based European studies (FINRISK, DanMONICA, Moli-sani, Northern Sweden) of the BiomarCaRE consortium, the association of incident HF with mortality, the relation of cardiovascular risk factors, prevalent cardiovascular diseases and biomarkers (C-reactive protein, CRP; N-terminal pro B-type natriuretic peptide, Nt-proBNP) and their attributable risks were tested in women vs. men.

Results: Over a median follow-up of 12.7 years, fewer HF cases were observed in women (N=2399, 5.9%) than in men (N=2771, 7.3%). HF incidence increased markedly after the age of 60 years, initially with a more rapid increase in men, while women exceeded men after age 85. HF onset substantially increased mortality risk in both sexes.

Multivariable-adjusted Cox models showed sex differences for the association with incident HF: systolic blood pressure, hazard ratio per standard deviation in women 1.09 (1.05-1.14) vs. 1.19 (95% CI 1.14-1.24) in men; heart rate 0.98 (0.93-1.03) in women vs. 1.09 (1.04-1.13) in men; CRP 1.10 (1.00-1.20) in women vs. 1.32 (1.24-1.41) in men; and Nt-proBNP 1.54 (1.37-1.74) in women vs. 1.89 (1.75-2.05) in men.

Population-attributable risk of all risk factors combined was 59.0% in women, 62.9% in men.

Conclusions: Women had a lower HF risk than men. Sex differences were seen for systolic blood pressure, heart rate, CRP and Nt-proBNP with a lower HF risk in women.

Key words: heart failure, sex, epidemiology, cohort, biomarkers, mortality

Abbreviations list: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; FU, follow-up; HR, hazard ratio; HF, heart failure; Nt-proBNP, N-terminal pro B-type natriuretic peptide; PAR, population attributable risk; RRR, relative risk ratio; SD, standard deviation

INTRODUCTION

Heart failure (HF) is a growing epidemic worldwide associated with significant morbidity, mortality and health care costs in both sexes.(1) To improve HF prevention, the epidemiology and risk factors of HF need to be understood and differences between sexes require consideration.

Women and men differ in disease distribution, risk factors and outcome of HF. The sex-specific incidence of HF varies according to study population characteristics.(2,3) HF hospitalizations are more frequent in men than in women.(4) Women are hospitalized in more advanced HF states than men.(5) There is a number of established risk factors that significantly contribute to the population burden of HF. Among them, the distribution of arterial hypertension, obesity, blood lipids, diabetes, smoking, alcohol consumption, and prevalent cardiovascular diseases have been shown to differ by sex.(6-8) In addition, circulating biomarker concentrations related to the disease typically differ by sex, e.g. high-sensitivity C-reactive protein (CRP) and N-terminal pro B-type natriuretic peptide (Nt-proBNP).(9,10) The relevance of these known sex-differences in circulating biomarkers for the association with incident HF remains unknown.

HF prognosis is poor in both sexes.(11) Despite advances in therapy and management, the number of any-mention deaths attributable to HF was approximately as high in 1995 as it was in 2013.(12) Evidence suggests that death rates for HF are higher for men than for women.(12)

In the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) consortium, we systematically examined the sex-specific epidemiology of HF incidence, the role of classical cardiovascular risk factors, circulating biomarkers, and their population attributable risks (PAR). The risk of mortality after new-onset HF according to sex was determined.

METHODS

Study sample

Our prospective cohort study uses a subcohort of the BiomarCaRE consortium, which harmonizes risk factors, biomarker measurements and endpoints from European community-based cohorts.(13) Information on HF status at baseline and follow-up was available in four cohorts DanMONICA, FINRISK, Moli-sani and Northern Sweden (baseline examinations between years 1982 and 2010) in 78657 individuals. Participants with self-reported and/or physician-diagnosed history of HF and/or prior ICD-10 coding for HF at baseline were excluded from analyses (N=1582). Details on the enrolment and follow-up procedures for each study separately are provided in the **Supplemental Material**.

Local Ethics Committees approved all participating studies.

Risk factors and follow-up

Risk factor information was collected at the baseline visits. The variables body mass index (BMI), systolic blood pressure, total cholesterol were measured locally by routine methods according to the WHO MONICA protocol (http://www.thl.fi/monica/). Information on smoking was obtained by self-report and collected locally in the study centers. Diabetes, anti-hypertensive medication, history of stroke, and myocardial infarction were centrally harmonized in the MORGAM (MONICA Risk, Genetics, Archiving and Monograph) project.(14) Average alcohol consumption was assessed in grams per day and classified to the WHO average volume drinking categories (http://www.who.int/publications/cra/en/). As 'abstainers' could not be separated from the 'average drinking category I', we merged these two categories.

HF diagnosis was based on questionnaire information and national hospital discharge registry data, including data on ambulatory visits to specialized hospitals. In addition, cause of death registry data were screened for incident HF as a comorbidity of individuals that died with other causes (http://www.thl.fi/publications/morgam/cohorts/index.html). Mortality data were derived from central death registries. The survey period from baseline examination to follow-up was between 1982 and 2010 for all cohorts. The last follow-up was between 2010 and 2011 in the different cohorts (detailed information by study cohort is provided in the **Supplemental Material**).

Biomarker measurement

Biomarker measurements from stored blood samples were available for most of the cohorts (**Supplemental Table 1a**). CRP was determined by latex immunoassay (Abbott, Architect c8000), with intra-assay and interassay coefficients of variation of 0.93 and 0.83,(15) and available in 37644 individuals. Nt-proBNP was measured on the ELECSYS 2010 platform using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics). Information on Nt-proBNP was available in 30443 individuals. The analytical range is given as 5–35000 ng/L. Intra- and interassay coefficients of variation were 2.58 and 1.38.

Statistical analysis

Missing data were handled by available case analyses, e.g. for each computation, only those without missing values on the variables involved in that particular analyses were used. Continuous variables are presented as median (25^{th}, 75^{th} percentile) and binary variables as absolute and relative frequencies. Prevalent HF cases were excluded from all analyses (N=1582, **Supplemental**

Table 9). Survival analyses used the 'time-to-HF diagnosis'. The Aalen-Johansen estimator was used in computing cumulative incidence curves for HF and death before HF as competing risks. Cumulative incidence curves were also computed for HF and myocardial infarction as competing risks. To examine the association of incident HF and all-cause mortality, a sex and cohort stratified Cox regression for all-cause mortality with HF, atrial fibrillation (AF) and cardiovascular disease during follow-up as time dependent covariates was computed. A second model including also BMI, systolic blood pressure, antihypertensive medication, total cholesterol, diabetes, and daily smoking was computed, these variables were used as time fixed covariates as they were only available at baseline. For all these covariates and HF, AF and cardiovascular disease, a sex interaction was included in the model to allow for the effect of the covariate to vary by sex. Age was used as the time scale in all models.

Sex and cohort stratified Cox regressions were performed to examine the associations of HF risk factors in women and men with incident HF. Cubic splines were used to explore the linearity of the association of continuous variables with time-to-HF. First, for each risk factor a Cox model was computed. Then a model including simultaneously BMI, systolic blood pressure, antihypertensive medication, total cholesterol, diabetes, and daily smoking (and estimated glomerular filtration rate (eGFR) in a refining analysis) was fitted. Each of the variables heart rate (HR), alcohol consumption, history of myocardial infarction, history of stroke, CRP, and Nt-proBNP were added in turn to this last model, which we call the base model. For all covariates, a sex interaction was included in each model. Whenever a model included systolic blood pressure, antihypertensive medication was also part of the model. In a refining analysis, for each covariate in the base model an interaction with age categories was included to obtain sex and age specific

HRs for each covariate of interest. To the base model we further added Nt-proBNP and AF during follow-up together with sex interaction terms. In the data used for this last model there were 84 individuals with HF and AF diagnosed at the same time during follow-up. For these observations, the onset of AF was treated as occurring shortly before HF. Relative risk ratios (RRR) for the women:men ratio of hazard ratios and population attributable risks (PAR) for incident HF were calculated. The proportional hazard assumption was examined graphically and with formal tests using the methods described in Grambsch et al.(16). No major deviations from this assumption were observed.

For the PAR calculations, categorization of the continuous variables BMI (<25 kg/m², 25 to <30 kg/m², ≥30kg/m²), systolic blood pressure (<120 mm Hg, 120 to <140 mm Hg, 140 to <160 mm Hg, ≥160 mm Hg), and total cholesterol (cut-off 200 mg/dL=5.17 mmol/L) were performed. P-values were not corrected for multiple testing and are provided for descriptive purposes.(17)

R statistical software version 3.4.1 (www.R-project.org) was used to perform all statistical analyses. A more detailed description of the statistical methods is provided in the **Supplemental Material.**

RESULTS

Baseline characteristics

At baseline, our study sample had a median age of 49.4 years with an age range of 24.1 to 98.7 years. 40656 (51.7%) of the participants were women. Median age was similar for women and men (49.0 vs. 49.9 years). Baseline characteristics of the study sample by sex are shown in **Table 1**. Overall, women had a more preferable cardiovascular risk factor profile than men with a lower BMI, lower systolic blood pressure, lower total cholesterol and a lower prevalence of diabetes, cigarette abuse and daily alcohol consumption. Heart rate was higher in women than in men. Women were less likely to have a history of prevalent cardiovascular disease (including stroke and myocardial infarction) than men. CRP concentration did not differ by sex. Nt-proBNP levels were higher in women than in men.

Study characteristics by cohort are shown in **Supplemental Table 1a**. Missing value information of baseline characteristics according to cohort (**Supplemental Table 1b**) and sex (**Supplemental Table 1c**), and regarding missingness of Nt-proBNP (**Supplemental Table 1d**) and CRP (**Supplemental Table 1e**) are also shown in the **Supplemental Material**.

HF incidence and mortality by sex

Over a median follow-up of 12.7 years, range 0-29 years, less incident HF cases were observed in women (N events=2399, 5.9%) than in men (N events=2771, 7.3%) (for follow-up information by cohort please see **Supplemental Table 2**). Cumulative incidence curves for HF and death before HF as a competing risk are shown in **Figure 1** (cumulative incidence curves for HF by cohort are shown in **Supplemental Figure 1a**, and for HF and myocardial infarction in **Supplemental**

Figure 1b). HF incidence was very low in both sexes before the age of 60 years. After 60 years, HF incidence increased markedly initially with a more rapid increase in men. More men died before they could develop HF (**Figure 1**, solid lines). At the age of 85 years, cumulative incidence curves crossed with women then exceeding men in HF incidence (**Figure 1**, dashed lines). Lifetime risk was about 38% in both sexes at the age of 90 years (**Supplemental Table 3**).

In both age-adjusted and risk factor adjusted models, incident HF increased the risk of death more than 5-fold in both sexes (**Figure 2**).

Sex interactions in HF risk factors

Multivariable-adjusted HRs for HF by sex and the respective interaction P values are shown in **Table 2**. Except for total cholesterol in men, where no association with HF could be shown, all classical cardiovascular risk factors, a history of myocardial infarction and stroke, and the biomarkers CRP and Nt-proBNP were associated with new onset HF in women and men. We observed significant sex interactions in the association of systolic blood pressure, heart rate, CRP and Nt-proBNP with incident HF with a lower magnitude of association in women than in men (**Table 2**).

The results for multivariable-adjusted Cox regression models after exclusion of individuals with prevalent cardiovascular diseases are shown in **Supplemental Table 4**. Results did not change markedly. Age-adjusted Cox regression models are shown in **Supplemental Table 5.** Examination of the results by survey decade revealed no relevant differences in the association of cardiovascular risk factors and incident HF. (**Supplemental Table 6a**) An age-interaction was seen for the association of systolic blood pressure with incident HF in individuals between 45 and 54 years of

age with a higher risk in men. (**Supplemental Table 6b**) After including eGFR in the base model, the sex interaction of systolic blood pressure and heart rate with incident HF was no longer statistically significant. (**Supplemental Table 7**) There was no interaction by Nt-proBNP level in the association of BMI and incident HF. (**Supplemental Table 8**) Combining Nt-proBNP and AF during follow-up in one equation, we did not see a statistically significant sex interaction (interaction P value=0.53; analysis not shown).

Population-attributable risks by risk factors and sex

Population-attributable risks (PARs) for 5-year HF incidence resulting from the classical risk factors are presented in **Figure 3.** PARs additionally including heart rate are shown in **Supplemental Figure 2**. The overall PAR of all risk factors combined (BMI, systolic blood pressure, total cholesterol, daily smoking, diabetes, history of myocardial infarction and stroke) was 59.0% for women and 62.9% for men. Highest PARs were seen for obesity and systolic blood pressure in both sexes with highest attributable risk for obese women and hypertensive men.

DISCUSSION

Across four European community cohorts, women had a lower risk for incident HF than men in middle-aged to older individuals whereas women exceeded men in HF risk in the oldest age groups. Lifetime risk was up to 38% when individuals reached the age of 90 years. Incident HF increased the risk of mortality more than 5-fold with no significant sex difference. Among clinical variables, increased systolic blood pressure, heart rate, CRP, and Nt-proBNP carried a lower risk of HF in women than in men. PARs from classical risk factors were largely comparable in both sexes with highest attributable risk for obese women and hypertensive men.

HF is an age-dependent disease, showing a clear sex-specific incidence. Consistent with prior reports,(18,19) overall HF incidence was lower in women than in men. Whereas men developed HF earlier than women in middle-aged to older age groups, women revealed a higher HF incidence in the oldest old. Death was a stronger competing risk in men. Our data confirm similar trends observed in US cohorts.(20) HF-related mortality is still high despite public health strategies to reduce risk factor levels.(11) Although there is evidence of lower mortality rates in women in a 3-year follow-up,(10) we found no differences in mortality risk by sexes during our long follow-up. As women develop HF later than men, the initial survival benefit of women seems to be diminished in the long-term. In our study, incident HF was associated with a more than 5-fold increased mortality risk in both sexes and calls for improved therapies and management.

Elevated BMI and obesity are among the most relevant HF risk factors.(21) They are also related to other risk factors such as arterial hypertension or cardiovascular diseases which themselves carry a high risk for new onset HF. In line with other studies,(22,23) we could confirm a strong relationship between BMI and incident HF with no significant sex interaction. Of all the examined

risk factors, obesity showed the highest 5-year PARs for new onset HF with obese women being at highest risk. BMI is a modifiable risk factor and HF prevention strategies should focus on weight loss with a BMI target of <25kg/m^2. At the population level, weight control in women may have higher prognostic relevance due to the PAR of more than 30% compared to 22% in men.

Arterial hypertension plays a major role in the development of HF and carries a high risk for related cardiovascular events.(24) The Framingham Heart Study showed a doubling of HF risk in individuals with blood pressure >160/90 mmHg compared to those <140/90mmHg.(3) Evidence from the Framingham cohort and the Cardiovascular Health Study showed that the association of systolic blood pressure with incident HF was stronger in women than in men.(6,25) In contrast, we found a higher HF risk in men with elevated blood pressure accounting for antihypertensive medication. Interestingly, the association of blood pressure and incident HF may be even stronger in middle-aged men. It is known that men have a higher risk of hypertension-related cardiac diseases such as myocardial infarction and atrial fibrillation.(26) Since HF often develops as a consequence of these diseases, the observed higher HF risk in men may be related to elevated blood pressure. However, since antihypertensive therapy leads to a significant reduction in cardiovascular events and deaths,(27) all individuals at risk should receive targeted blood pressure control to prevent HF and its sequelae.

Elevated resting heart rate is a known predictor of cardiovascular risk.(28) Increased heart rate independently predicts HF,(29) HF hospitalizations and cardiovascular mortality.(30) Our female study population had a higher median heart rate at baseline as seen in prior data(31), but increased heart rate was more hazardous for men with no significant association in women. These results are consistent with prior studies that showed a steeper risk gradient for all-cause mortality in men.(32)

In most studies, the association of heart rate with cardiovascular outcomes was stronger in men or even confined to men.(33,34) Using a large community-based study sample, increased heart rate was associated with HF incidence in initially healthy men. Different mechanisms that may explain the sex-specific association between heart rate with cardiovascular disease have been proposed including increased heart rate as a sign of sympathetic overactivity in men and its adverse effects on the development of the metabolic syndrome and insulin resistance.(31)

Biomarkers have increased our understanding of the pathophysiology of HF. Increased levels of inflammatory biomarkers have consistently been related to increased HF risk(35) and mortality.(36) In the MESA study, high CRP levels were related to progressive deterioration of myocardial function irrespective of age and sex.(37) The role of inflammation for the development of coronary artery disease, which often precedes HF, is well known.(38) Most of the common cardiovascular risk factors that were more prevalent in men in the current study, are related to increased inflammatory activity mirrored by elevated CRP levels.(39) We and others(40) found a strong association of CRP and HF risk in men that may be an expression of a higher proinflammatory state in men compared to women.

Prior studies demonstrated that Nt-proBNP provides an incremental prognostic value for incident HF beyond the classical risk factors.(10) Nt-proBNP levels in our cohort were higher in women than in men. Female sex has been described as a strong predictor of elevated natriuretic peptides.(9) In relation to incident HF, Nt-proBNP was a stronger predictor of risk in men compared to women. Elevated Nt-proBNP levels have shown a stronger association with incident HF with reduced ejection fraction(41) which is more common in men(42). This fact may explain the stronger association observed in men in our study population.

Limitations and strengths

Due to the epidemiologic nature of our data, pathophysiological mechanisms of the observed sex interactions cannot be fully explained.

Besides ICD-based HF ascertainment in all cohorts, HF diagnosis was additionally accepted via self-report in FINRISK and Moli-sani. We cannot provide information on HF subtypes (HF with preserved and reduced ejection fraction) as this depth of phenotypic classification was not collected consistently in the BiomarCaRE cohorts. Since HF with preserved ejection fraction often remains undetected, in particular in the outpatient sector,(43) we assume a predominance of HF with reduced ejection fraction which may have led to an underdiagnosis of HF in women. Overall, the specificity of HF data in the cohorts has been shown to be good with limitations in sensitivity(44) with a possible bias towards more severe HF cases. Since prevalent HF cases were removed before computing incidences, the latter may be slightly underestimated. We are not able to relate prevalent AF to HF risk, as this variable is not reliable enough to be used in the current analyses. Additionally, information about prevalent chronic obstructive pulmonary disease was not available as a harmonized variable.

Information on biomarkers and heart rate was only available in a subcohort of the study sample. However, the number of individuals with biomarker measurements was still large enough to provide reliable estimates. As usual in community-based studies, residual confounding cannot be excluded and is very likely.

The cohorts are formed by the respondents of surveys based on random population samples. Possible selective survey non-participation, in particular if different for men and women, may have biased the results.

Some of the baseline data are several decades old, which permitted us to examine long-term incidence of the lifetime disease HF up to oldest age groups. Risk factor information was available at baseline only. However, we could demonstrate that classical risk factor associations by sex are strong and similar across cohorts whether in older samples or cohorts with more recent enrolment or whether from Northern or Southern Europe. As we present data from Northern and Southern Europe, our study mainly includes Caucasian participants. That limits, at least in part, the generalizability(45) of our findings to other racial or ethnic groups.

Strengths of the study are the large size of the community-based cohorts using harmonized risk factors and endpoints with sufficient power to examine sex interactions.

CONCLUSIONS

In conclusion, our data provide evidence that part of the sex differences in HF incidence may be explained by sex-specific distribution and association of classical risk factors. Importantly, a large proportion of HF risk can be attributed to classical cardiovascular risk factors with overweight and obesity highlighted as key factors on HF incidence in both sexes. Our population-based data indicate that weight control should be equally recommended to overweight and obese women and men. We found significant sex differences in the association of systolic blood pressure, heart rate, and the biomarkers CRP and Nt-proBNP with a higher risk of HF in men than in women. If sex-specific blood pressure and heart rate targets or biomarker guided therapy regimens may reduce HF incidence and mortality needs further investigation. The pathophysiology accounting for our observations requires further biological investigation. Considering the epidemic dimension of HF in aging populations, understanding sex differences in HF risk is crucial for developing long-term preventive measures to reduce mortality, public health burden and healthcare costs related to HF in both, women and men.

CLINICAL PERSPECTIVES

What is new?

- In European community cohorts, overall heart failure (HF) risk was lower in women than in men while women exceeded men in the oldest age groups.
- Incident HF increased the risk of mortality more than 5-fold in both sexes.
- Sex interactions were seen for systolic blood pressure, heart rate, C-reactive protein and N-terminal pro B-type natriuretic peptide with a lower HF risk in women.
- Among the classical risk factors, obesity explained the largest proportion of the attributable risk in both sexes.

What are the clinical implications?

- HF is a frequent disease with high mortality risk.
- At the community level, modification of risk factors such as weight control seems to be crucial for women and men, while smoking cessation and strict blood pressure control may be even more important for men than for women.
- Observed sex differences in classical risk factors and biomarkers have to be evaluated for their pathophysiological mechanisms and sex specific prevention strategies.

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Figure Titles and Legends

Central Illustration. Heart failure incidence, risk factors and mortality in the community.

*The relative incidence is derived from the weighted integrated ratio of the cumulative incidence curves in men over women between ages 35 to 95.

CRP, C-reactive protein; Nt-proBNP, N-terminal pro B-type natriuretic peptide.

Figure 1. Cumulative incidence curves for incident heart failure and death without heart failure in women and men. Incident heart failure and death were treated as competing risks. The numbers of individuals at risk are provided under the figure. Only curves until the age of 95 years are shown.

Figure 1.

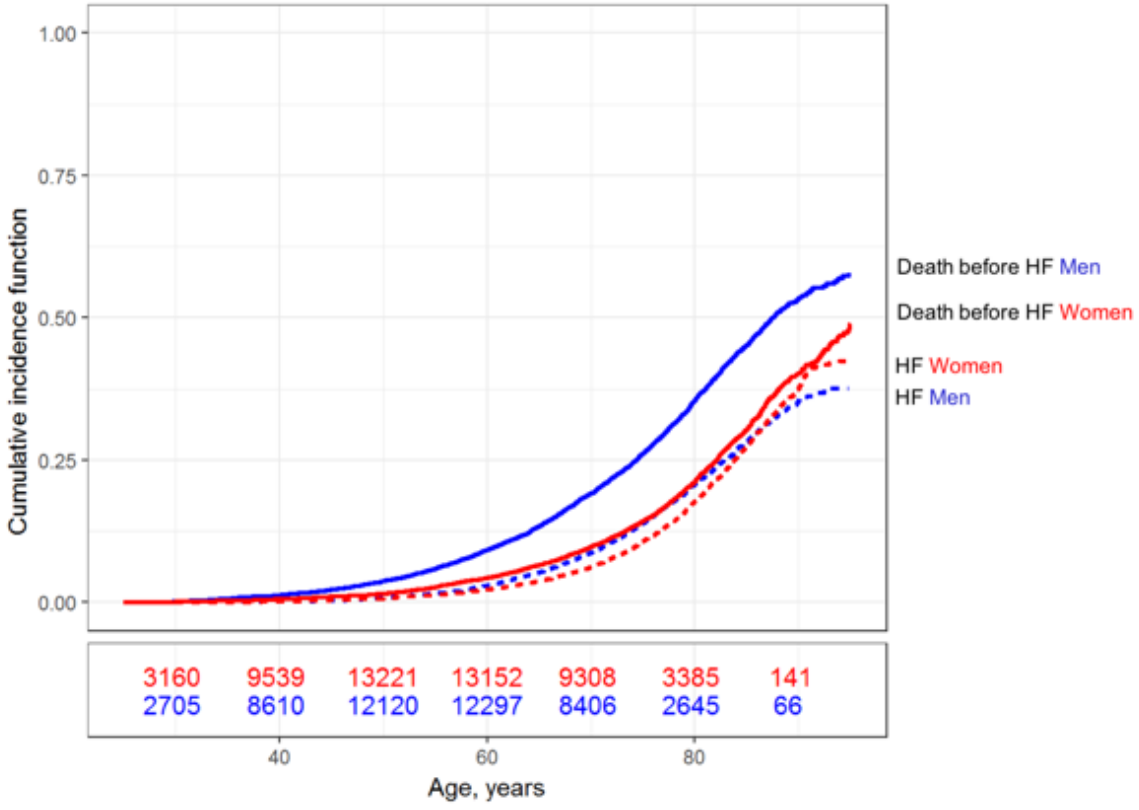


Figure 2. Cox regression analyses for all-cause mortality with heart failure, atrial fibrillation and cardiovascular disease during follow-up as time-dependent covariates, model 1 (age-adjusted). Model 2 is additionally adjusted for body mass index, systolic blood pressure, diabetes, daily smoking, antihypertensive medication, total cholesterol. The x-axis is shown on a log-scale. Continuous variables were modeled using quadratic terms, with the exception of age which was used as the time scale.

N available men: 36247, N available women: 38880.

SD standard deviation, CI Confidence Interval.

Figure 2.

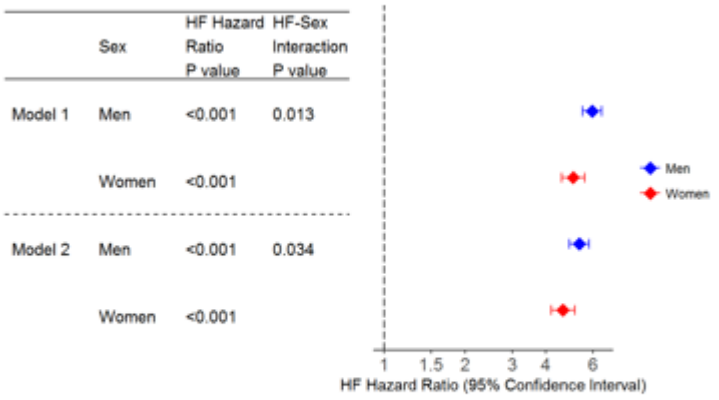
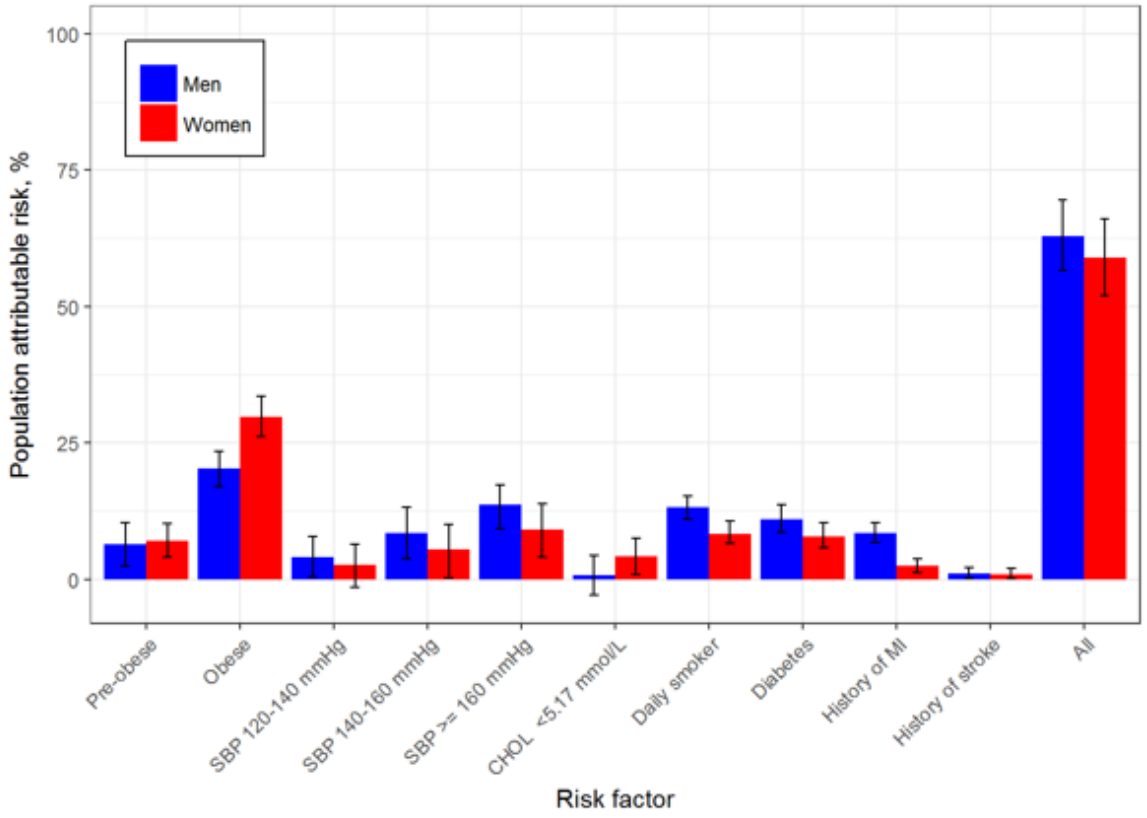


Figure 3. Population attributable risks for 5-year incidence of heart failure. The N events/N used in the computation of the models were N=2496/34547 (men) and 2158/37112 (women). Confidence intervals were computed using the bootstrap (with 500 iterations). CHOL stands for total cholesterol, SBP for systolic blood pressure. The regression models used in the estimation of the PARs include all the risk factors shown above and antihypertensive medication.

Figure 3.



Tables

Table 1. Baseline characteristics of the study sample by sex.

	Women **N=40656**	**Men** **N=38001**
Age at examination (years)	49.0 (39.4, 58.9)	49.9 (39.8, 59.9)
Body mass index (kg/m²)	25.6 (22.8, 29.4)	26.7 (24.3, 29.4)
Systolic blood pressure (mmHg)	130 (118, 146)	136 (125, 150)
Antihypertensive medication No. (%)	6474 (16.7)	5989 (16.5)
Total cholesterol (mmol/L)	5.6 (4.89, 6.4)	5.61 (4.9, 6.4)
Diabetes No. (%)	1682 (4.1)	1955 (5.2)
Daily smoking No. (%)	8460 (21)	10752 (28.6)
Average daily alcohol consumption (g)	1 (0, 6)	9 (1, 23)
Average drinking category I No. (%)	37332 (94.6)	32294 (87.9)
Average drinking category II No. (%)	1777 (4.5)	2789 (7.6)
Average drinking category III No. (%)	342 (0.9)	1655 (4.5)
Heart rate (bpm)	69 (63, 76)	66 (60, 74)
History of myocardial infarction No. (%)	393 (1)	1313 (3.5)
History of stroke No. (%)	404 (1)	610 (1.6)
C-reactive protein (mg/L)	1.4 (0.6, 3.2)	1.4 (0.7, 2.9)
Nt-proBNP (ng/mL)	58 (33, 99)	32 (15, 69)
eGFR (mL/min/1.73 m^2)	93.1 (79.3, 105.8)	93.6 (80.6, 105.6)

Continuous variables are presented as median (25^{th}, 75^{th} percentile), binary variables as absolute and relative frequencies. N incident HF: All=5,170 (6.6%), women=2,399 (5.9%), men=2,771 (7.3%).

Average drinking categories based on pure alcohol intake: category I, for women 0-19.99 g/day, for men 0-39.99 g/day; category II, for women 20-39.99 g/day, for men 40-59.99 g/day; category III, for women ≥40 g/day, for men ≥60 g/day.

C-reactive protein was available in a subgroup of 37644 individuals, N-terminal pro B-type natriuretic peptide (Nt-proBNP) in 30443. eGFR was only available in 37602 individuals.

Table 2. Multivariable-adjusted hazard ratios for incident heart failure by sex and interaction P values for heart failure risk factors in the overall sample.

Variable	Interaction P value	Sex	Hazard Ratio (95% Confidence Interval)	P value	Relative Risk Ratio Women/Men (95% Confidence Interval)	N available
Body mass index (kg/m^2)	0.79	Women	1.43 (1.38, 1.48)	<0.001	0.99 (0.94, 1.05)	38197
		Men	1.44 (1.38, 1.50)	<0.001		35606
Systolic blood pressure (mm Hg)	**0.004**	Women	1.09 (1.05, 1.14)	<0.001	0.92 (0.86, 0.97)	38197
		Men	1.19 (1.14, 1.24)	<0.001		35606
Antihypertensive medication	0.89	Women	1.49 (1.34, 1.64)	<0.001	1.01 (0.88, 1.16)	38197
		Men	1.47 (1.33, 1.61)	<0.001		35606
Total cholesterol (mmol/L)	0.22	Women	0.95 (0.91, 0.99)	0.027	0.96 (0.91, 1.02)	38197
		Men	0.99 (0.95, 1.03)	0.60		35606
Diabetes	0.23	Women	1.87 (1.63, 2.15)	<0.001	0.89 (0.74, 1.07)	38197
		Men	2.09 (1.85, 2.36)	<0.001		35606
Daily smoking	0.70	Women	1.98 (1.77, 2.23)	<0.001	1.03 (0.89, 1.19)	38197
		Men	1.93 (1.77, 2.10)	<0.001		35606
Alcohol consumption	0.11	Women	0.95 (0.89, 1.02)	0.13	0.94 (0.87, 1.01)	37168
		Men	1.01 (0.97, 1.06)	0.52		34607
Heart rate	**<0.001**	Women	0.98 (0.93, 1.03)	0.36	0.90 (0.84, 0.96)	29430

Variable	Interaction P value	Sex	Hazard Ratio (95% Confidence Interval)	P value	Relative Risk Ratio Women/Men (95% Confidence Interval)	N available
History of myocardial infarction	0.08	Men	1.09 (1.04, 1.13)	<0.001	0.80 (0.63, 1.03)	26974
		Women	1.86 (1.50, 2.31)	<0.001		38159
		Men	2.32 (2.05, 2.63)	<0.001		35554
History of stroke	0.73	Women	1.39 (1.07, 1.81)	0.013	0.94 (0.67, 1.32)	38168
		Men	1.48 (1.20, 1.83)	<0.001		35582
C-reactive protein (mg/L)	**0.002**	Women	1.10 (1.00, 1.20)	0.043	0.83 (0.75, 0.93)	18935
		Men	1.31 (1.23, 1.41)	<0.001		17568
Nt-proBNP (ng/mL)	**0.006**	Women	1.54 (1.37, 1.74)	<0.001	0.83 (0.73, 0.95)	15465
		Men	1.89 (1.75, 2.05)	<0.001		14098

The first six variables represent our base model, the others are separately added on top to the base model. All models include body mass index, systolic blood pressure, antihypertensive medication, total cholesterol, diabetes, and daily smoking. Biomarker information was available in a subgroup only (**Supplemental Table 1a**).

Hazard ratios for continuous variables are for one standard deviation increase, body mass index: 4.65 kg/m², systolic blood pressure: 21 mm Hg, total cholesterol: 1.17 mmol/L, heart rate: 12 bpm, log(C-reactive protein, mg/L): 1.1, log(Nt-proBNP, ng/mL): 0.98, transformed alcohol consumption: 1.36. Standard deviations were computed using all observations regardless of sex.

C-reactive protein, Nt-proBNP and alcohol consumption were log-transformed. Since alcohol consumption can equal zero, one was added before applying the transformation.

Nt-proBNP N-terminal pro B-type natriuretic peptide.